No. 2025-1236

UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

EXELIXIS, INC.,

Plaintiff-Appellee,

v.

MSN LABORATORIES PRIVATE LTD., MSN PHARMACEUTICALS, INC.,

Defendants-Appellants.

On Appeal from the United States District Court for the District of Delaware in Case No. 1:22-cv-00228-RGA, Judge Richard G. Andrews

BRIEF FOR PLAINTIFF-APPELLEE EXELIXIS, INC.

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June 11, 2025

PATENT CLAIMS AT ISSUE

U.S. Patent No. 11,091,439, Claim 4

4. The N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N′-(4-fluorophenyl) cyclopropane-1,1-dicarboxamide, malate salt according to claim 3, wherein said salt is the (L)-malate salt.

Claim 4 depends from the following claims:

1. N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N′-(4-fluorophenyl) cyclopropane-1,1-dicarboxamide, malate salt, wherein said salt is crystalline.

3. The N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N′-(4-fluorophenyl) cyclopropane-1,1-dicarboxamide, malate salt according to claim 1, wherein said salt is the (L)-malate salt or (D)-malate salt.

U.S. Patent No. 11,091,440, Claim 3

3. A pharmaceutical composition comprising the N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxylphenyl)-N′-(4-fluorophenyl) cyclopropane-1,1-dicarboxamide, malate salt, wherein said salt is the (L)-malate salt or (D)-malate salt and wherein said salt is crystalline; and a pharmaceutically acceptable excipient.

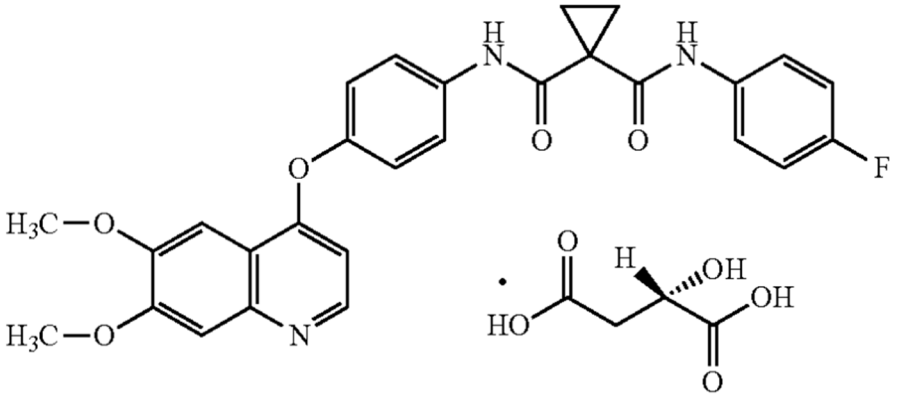
U.S. Patent No. 11,098,015, Claim 2

2. A method of treating cancer, comprising administering to a subject in need thereof N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N′-(4-fluorophenyl) cyclopropane-1,1-dicarboxamide, malate salt, wherein said salt is the (L)-malate salt or the (D)-malate salt, said salt is crystalline, and said cancer is kidney cancer.

U.S. Patent No. 11,298,349, Claim 3

3. A pharmaceutical composition for oral administration comprising Compound IB;

IB



one or more fillers; one or more disintegrants; one or more glidants; and one or more lubricants, wherein the pharmaceutical composition is a tablet or capsule pharmaceutical composition; and

wherein the pharmaceutical composition is essentially free of 6,7-dimethoxy-quinoline-4-ol.

CERTIFICATE OF INTEREST

Counsel for Plaintiff-Appellee Exelixis, Inc. certifies the following:

1. Represented Entities. Fed. Cir. R. 47.4(a)(1). Provide the full names of all entities represented by undersigned counsel in this case.

Exelixis, Inc.

2. Real Party in Interest. Fed. Cir. R. 47.4(a)(2). Provide the full names of all real parties in interest for the entities. Do not list the real parties if they are the same as the entities.

None.

3. Parent Corporations and Stockholders. Fed. Cir. R. 47.4(a)(3). Provide the full names of all parent corporations for the entities and all publicly held companies that own 10% or more stock in the entities.

None.

4. Legal Representatives. List all law firms, partners, and associates that (a) appeared for the entities in the originating court or agency or (b) are expected to appear in this court for the entities. Do not include those who have already entered an appearance in this court. Fed. Cir. R. 47.4(a)(4).

WILMER CUTLER PICKERING HALE AND DORR LLP: Timothy A. Cook, Jonathan A. Cox, Katherine P. Kieckhafer (former), Marissa A. Lalli, William F. Lee, Amy L. Mahan, Cristina Salcedo, Labdhi Sheth (former), Emily R. Whelan, Kevin M. Yurkerwich (former)

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5. Related Cases. Other than the originating case(s) for this case, are there related or prior cases that meet the criteria under Fed. Cir. R. 47.5(a)?

[X] Yes (file separate notice; see below) [ ] No [ ] N/A (amicus/movant)

If yes, concurrently file a separate Notice of Related Case Information that complies with Fed. Cir. R. 47.5(b). Please do not duplicate information. This separate Notice must only be filed with the first Certificate of Interest or, subsequently, if information changes during the pendency of the appeal. Fed. Cir. R. 47.5(b).

Already filed.

6. Organizational Victims and Bankruptcy Cases. Provide any information required under Fed. R. App. P. 26.1(b) (organizational victims in criminal cases) and 26.1(c) (bankruptcy case debtors and trustees). Fed. Cir. R. 47.4(a)(6).

None.

Dated: June 11, 2025

/s/ Thomas G. Saunders

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CASES

STATEMENT OF RELATED CASES

This case has not previously been before this Court or any other appellate court. The following cases involve or involved one or more of the same patents as this appeal from *Exelixis, Inc. v. MSN Laboratories Private Ltd.*, No. 1:22-cv-00945 (D. Del.): *Exelixis, Inc. v. Teva Pharmaceuticals Development, Inc.*, No. 1:22-cv-01168 (D. Del.); *Exelixis, Inc. v. Cipla Ltd.*, No. 1:23-cv-00287 (D. Del.); *Exelixis, Inc. v. Cipla Ltd.*, No. 1:24-cv-00565 (D. Del.); *Exelixis, Inc. v. Sun Pharmaceutical Industries Ltd.*, No. 1:24-cv-01208 (D. Del.); *Exelixis, Inc. v. Biocon Pharma Ltd.*, No. 1:25-cv-00452 (D. Del.); *Exelixis, Inc. v. Azurity Pharmaceuticals, Inc.*, No. 1:25-cv-00478 (D. Del.); and *Azurity Pharmaceuticals, Inc. v. Exelixis, Inc.*, IPR2025-00210 (P.T.A.B.).

The following cases involve a different patent owned by Plaintiff Exelixis, Inc. ("Exelixis") and could be affected by this Court's decision in the pending appeal: *Exelixis, Inc. v. Sun Pharmaceutical Industries Ltd.*, No. 1:25-cv-00423 (D. Del.); *Exelixis, Inc. v. MSN Laboratories Private Ltd.*, No. 1:25-cv-00346 (D. Del.); and *Azurity Pharmaceuticals, Inc. v. Exelixis, Inc.*, IPR2025-00427 (P.T.A.B.).

INTRODUCTION

Exelixis is a global oncology company innovating treatments for some of the world's hardest-to-treat cancers. After discovering cabozantinib in 2003, Exelixis invested years in research and development before achieving a salt form and formulations that were stable, safe, and effective for patients. The resulting cabozantinib formulations, approved by the Food & Drug Administration ("FDA") as Cometriq® in 2012 and Cabometyx® in 2016, have become leading therapeutic drugs used to treat tens of thousands of kidney, liver, and thyroid cancer patients. The patents at issue protect Exelixis inventions that were instrumental in making cabozantinib a viable and effective cancer treatment.

U.S. Patent Nos. 11,091,439 ("'439 patent"), 11,091,440 ("'440 patent"), and 11,098,015 ("'015 patent") (together, "Malate Salt Patents") reflect Exelixis' invention of malate salts of cabozantinib, and particularly crystalline malate salts, which have advantages over other salts of cabozantinib, including improved stability and solubility. Appx129(7:31-8:25). U.S. Patent No. 11,298,349 ("'349 patent") reflects Exelixis' invention of a cabozantinib (L)-malate formulation essentially free of a genotoxic impurity that Exelixis discovered when developing cabozantinib for clinical use.

MSN Laboratories Private Limited and MSN Pharmaceuticals, Inc. (collectively, "MSN"), which seek to market generic versions of Cabometyx®,

challenged the asserted claims' validity on a variety of grounds. But after a bench trial featuring 15 witnesses and 122 exhibits, the district court concluded that MSN had not carried its burden of proving invalidity. On appeal, MSN rehashes factual arguments and attempts to manufacture legal error.

First, the district court did not err—let alone clearly err—in finding written-description support for the asserted claims of the Malate Salt Patents. Although MSN focuses on particular crystalline forms of cabozantinib (L)-malate that it contends are different from two specific polymorphs in the specification's working examples, the Malate Salt Patents' disclosure is not limited to those two examples. The specification (1) refers to crystalline (L)-malate salts generally, (2) provides the common chemical formula for the claimed compounds, (3) discloses that the salts are crystalline, i.e., have "a 'regular repeating underlying arrangement of molecules,'" Appx20 (quoting Appx1917(537:22-25)), and (4) teaches a person of ordinary skill in the art ("POSA") how to distinguish between crystalline and amorphous cabozantinib, Appx25 (citing Appx1918(542:10-25)); Appx2047(846:4-19); Appx2049(856:6-24); Appx2052(866:10-867:3)). Those undisputed facts sufficiently support the district court's finding that the specification discloses "structural features common to the members of the genus so that one of skill in the art can visualize or recognize the members of the genus."

Appx23 (quoting *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1350 (Fed. Cir. 2010) (en banc)).

MSN's contrary arguments misread this Court's case law and misstate the facts. On the law, MSN cites cases finding no written description where claims are defined by function and dwells on the alleged unpredictable properties of distinct polymorphs, but Exelixis has not defined its claimed crystalline cabozantinib (L)-malate by function or by any of the unclaimed polymorph properties MSN cites. Instead, the claimed invention is defined by undisputed common structure. MSN's position that this disclosure of common structure is insufficient where a salt claim covers multiple crystalline polymorphs is not the law and would threaten countless claims covering pharmaceutical salts.

On the facts, the court found that, far from covering a "virtually infinite" genus, Br. 48, "[t]he maximum potential size of any pure polymorph genus is fourteen forms." Appx21 (citing Appx1919(547:2-5)). And MSN's attempt to paint Exelixis as improperly expanding its claims after failing to prove infringement of claims covering the specific polymorphic Form N-2 does not withstand the barest scrutiny: Not only were the Malate Salt Patents filed years before judgment in that litigation, but Exelixis filed claims to crystalline cabozantinib (L)-malate almost a ***decade*** before MSN even submitted its Abbreviated New Drug Application ("ANDA").

Second, as to the '349 patent, the district court also did not clearly err in finding non-obvious the claim to cabozantinib pharmaceutical formulations "essentially free" of a genotoxic impurity called the "1-1 impurity." MSN argued that the prior-art Brown process, when followed, inherently resulted in cabozantinib Active Pharmaceutical Ingredient ("API") "essentially free" of the 1-1 impurity, but the district court correctly rejected this argument as unsupported by the facts. Exelixis presented extensive evidence at trial that during the prior-art Brown synthesis, the 1-1 impurity formed as a degradation product from a synthetic intermediate, which led to uncontrolled levels of the impurity in the API. The 1-1 impurity was a starting material in the synthetic Brown process, but was not known to be a degradation product at the time and was not expected to remain in the final product. After discovering this problem, Exelixis worked for years to develop a new synthetic method, disclosed in the '349 patent, that avoids that degradation pathway and reliably yields cabozantinib essentially free of the 1-1 impurity. That evidence alone sufficiently supports the district court's finding that MSN failed to prove inherency—a demanding standard that requires MSN to show that the Brown process necessarily and inevitably results in cabozantinib essentially free of the 1-1 impurity.

MSN ignores that evidence and seeks to narrowly focus the Court on three batches of cabozantinib made by contract-manufacturer Regis, which it contends

used the Brown process and resulted in cabozantinib "essentially free" of the 1-1 impurity. But there was no clear error in the district court's finding that the process used to make these batches deviated from the Brown process in unknown ways, and therefore MSN had failed to meet its burden to show that Regis practiced the prior-art method. The record evidence includes an FDA submission explicitly stating that there were "processing and reagent changes" to the Brown synthetic route in the Regis batches upon which MSN relies, Appx3115(DTX-38, 9), and MSN's expert conceded that he did not know what the changes were and simply assumed they were minor, Appx1819(338:1-3). Such factual findings are the proper province of the district court, and there is no reason to disturb them on appeal.

MSN tries to manufacture legal error, complaining that the district court applied the wrong standard by requiring MSN to show that ***no*** 1-1 impurity formed, when the claims require only 200 parts per million (ppm) or less of the 1-1 impurity. The district court did no such thing: It noted MSN's argument that the evidence did not show a meaningful amount of 1-1 impurity and rejected it, citing evidence that an intermediate degraded to form 1-1 in large amounts and could not be controlled. Appx51.

STATEMENT OF ISSUES

1. Whether MSN fails to show clear error in the district court's factual finding that adequate written description supported the asserted claims of the Malate Salt Patents where the specification described structural features common to all crystalline cabozantinib (L)-malate salts.

2. Whether MSN fails to show clear error in the district court's finding that claim 3 of the '349 patent was non-obvious where MSN's argument depends on an inherency theory, and MSN failed to prove by clear and convincing evidence that performing the prior-art Brown process inherently resulted in cabozantinib (L)-malate "essentially free" of the 1-1 impurity.

STATEMENT OF THE CASE

I. EXELIXIS' PATENTS

Exelixis discovered the compound cabozantinib and spent years developing it into a safe and effective clinical product that is stable, bioavailable, and free of harmful genotoxic impurities. Appx1929-1932(587:18-597:9); Appx1925-1927(570:18-576:13-24); Appx1931(592:15-595:16). These innovations are the subject of the patents asserted in this case.

A. The Malate Salt Patents

After discovering cabozantinib, Exelixis determined that the free base form was unstable and unsuitable for development into a pharmaceutical product.

Appx1930(589:24-590:8). Among other research avenues, Exelixis and its contractor, Pharmorphix, attempted to stabilize cabozantinib through salt formation. Appx1927(577:18-578:3); Appx1930(591:2-11); Appx11021(PTX-87, 1). Pharmorphix tested 27 solvents for suitability and 22 acids for salt formation. Appx2036-2037(804:11-806:8); Appx11026(PTX-87, 6); Appx1938(622:15-21); Appx1930-1931(591:24-592:7); Appx11023(PTX-87, 3). For five of the resulting cabozantinib salts, including the (L)-malate salt, Exelixis tested bioavailability, photostability, and solubility in biorelevant media. Appx1930-1931(591:24-592:7); Appx11084(PTX-94, 21); Appx11218-11219(PTX-94, 155-156); Appx11225-11231(PTX-94, 162-168); Appx11236(PTX-94, 173); Appx11246-11248(PTX-94, 183-185).

The Malate Salt Patents are directed to the discovery that malate salts of cabozantinib, and crystalline forms of those malate salts, are particularly useful in pharmaceuticals. The first nonprovisional filing containing the disclosure of the Malate Salt Patents was in PCT/US2010/021194 ("'194 PCT application"), filed January 15, 2010. Appx94(JTX-1, 2); Appx9374-9415(JTX-7, 12-53). The original claims filed with that PCT application included:

> 1. [cabozantinib] malate salt.
>
> …
>
> 3. The [cabozantinib] malate salt according to claim 1, wherein said salt is a (L)-malate salt or a (D)-malate salt.

> 4. The [cabozantinib] malate salt according to claim 3, wherein said salt is the (L)-malate salt.
>
> …
>
> 6. The [cabozantinib] malate salt according to any one of claims 3 to 5, wherein said salt is crystalline.

Appx9413(JTX-7, 51). The original claims also included more specific claims to two crystalline polymorphs of crystalline cabozantinib (L)-malate—Forms N-1 and N-2. Appx9413-9414(JTX-7, 51-52).

In prosecuting this patent family, Exelixis chose to pursue narrow claims to Forms N-1 and N-2 first. The national phase application of the '194 PCT issued as U.S. Patent No. 8,877,776 ("'776 patent") on November 4, 2014, with claims to Form N-2 cabozantinib (L)-malate. U.S. Patent No. 9,809,549 ("'549 patent"), having the same specification as and claiming priority to the '194 PCT application, issued November 7, 2017, with claims to Form N-1 cabozantinib (L)-malate.

The Malate Salt Patents at issue here each claim priority to the '194 PCT application and have the same specification and expiration date. The '439 patent, filed October 14, 2020, claims the crystalline malate salts themselves, Appx94(JTX-1, 2); Appx141(JTX-1, 49); the '440 patent, filed May 13, 2021, claims pharmaceutical formulations of the salts, Appx143(JTX-2, 2); Appx190(JTX-2, 49); and the '015 patent, filed February 9, 2021, claims methods of treating cancer with the salts, Appx192(JTX-3, 2); Appx239(JTX-3, 49). Each

is subject to a terminal disclaimer limiting the patent's term to that of the original '776 patent. Appx6691(JTX-5, 393); Appx8785(JTX-6, 901); Appx9670(JTX-7, 308).

The Malate Salt Patents' common specification describes cabozantinib malate and includes six examples describing how to prepare both crystalline and amorphous cabozantinib malate. Appx134-137(18:59-24:47). The specification explains that "[t]his disclosure relate[s] to malate salts of [cabozantinib]," including "the (L)-malate salt of [cabozantinib], (Compound (I))." Appx128(6:56-61). The specification also discloses that "[t]he malate salts of [cabozantinib], and particularly Compound (I), have a preferred combination of pharmaceutical properties for development," including stability at various temperatures and humidities, reversible water uptake, and solubility. Appx129(7:10-13); *see* Appx2047-2048(848:20-851:10). Further, according to the common specification, "[t]he Compound (I) salt itself, and separately its crystalline and amorphous forms, exhibit beneficial properties over the free base and the other salts of [cabozantinib]," including crystallinity, solubility, and moisture sensitivity. Appx129(7:32-36 & Tbl.1). The specification explains that "[a]nother aspect of this disclosure relates to the crystalline forms" of cabozantinib (L)-malate and that "[e]ach of form of Compound (I) is a separate aspect of the disclosure." Appx129(8:26-30); Appx2048-2049(851:21-853:2). The specification further

describes two specific crystalline polymorphs—N-1 and N-2—in detail, including characterization by solid state ^{13}C NMR and x-ray powder diffraction. Appx130-131(9:63-11:57).

B. The '349 Patent

After inventing the cabozantinib malate salt, Exelixis made another important discovery: The known processes for synthesizing cabozantinib (L)-malate resulted in a product with variable and at times very high levels of a certain impurity: 6,7-dimethoxy-quinoline-4-ol (the "1-1 impurity"). Appx1933(600:19-601:4); Appx1925-1926(570:18-573:5); Appx1927(576:13-24).

Exelixis scientists initially used Process A to synthesize cabozantinib (L)-malate API, which included the initial "A-1 Process" and the modified "A-2 Process." Appx1932-1933(599:14-600:7, 602:1-9); Appx1925(568:2-569:25). The A-2 Process, also referred to as the "Brown process," is disclosed in Example 1 of Exelixis' International Patent Application No. WO 2010/083414 to Brown. Appx45.

Exelixis discovered that the A-2 Process, as performed by its contract manufacturers, produced API with widely varying levels of the 1-1 impurity. Appx1933(600:8-15). Although 1-1 was used as a starting material in the A-2 Process, it was not expected to remain in the final product because over 98% of the starting material is used up by the end of the first step, and each step of the five-

step process purifies the API. Appx52; Appx1949-1950(666:4-669:14); Appx2012-2013(708:23-709:14); Appx5852-5853(DTX-291, ¶¶[0099], [0102]). Upon further investigation, however, Exelixis discovered that the impurity was unexpectedly forming in the API, not as leftover starting material but rather as a degradation product during the synthetic process, including from an intermediate compound known as "1-3," Appx1933(600:8-601:4); Appx1925(569:16-25); Appx10845(PTX-35, 9), and again during the salt formation step, Appx1956(694:7-695:10), and yet again during and after formulation, Appx1934-1935(606:23-608:10). Exelixis also discovered that the 1-1 impurity was genotoxic, meaning it can damage DNA and cause cancer. Appx1925-1926(570:4-572:1); Appx1933-1934(600:8-604:20). It therefore became critical for Exelixis to devise a method of synthesizing and formulating cabozantinib (L)-malate that minimized levels of the 1-1 impurity in the ultimate product. Appx1933-1934(603:24-606:5).

Exelixis spent eight years developing the "B-2 Process," a novel process for synthesizing cabozantinib (L)-malate API detailed in the '349 patent. Appx1933-1935(602:1-606:5, 608:23-25); Appx1925-1927(570:18-573:5, 575:24-576:24). Exelixis' B-2 Process successfully reduced formation of the 1-1 impurity such that the API consistently has 200 ppm or less of the impurity (i.e., is "essentially free" of it). Appx1933-1934(603:24-606:5); Appx1936-1937(615:12-617:25); Appx45.

Exelixis uses the B-2 Process to commercially manufacture the API for Cabometyx® and Cometriq®. Appx1957(696:3-5); Appx1936(614:24-615:8); Appx10852(PTX-35, 16).

The '349 patent is directed to the invention of cabozantinib (L)-malate compositions essentially free of the 1-1 impurity. The specification identifies the 1-1 impurity and teaches that it should be minimized to ensure patient safety. Appx78(5:9-17); Appx86(22:8-27). The specification describes the synthetic steps of the B-2 Process and provides exemplary tablet and capsule formulations of cabozantinib (L)-malate. Appx86(21:37-22:27); Appx87-90(24:30-30:61); Appx78-79(5:24-7:9); Appx91(31:1-25). Claim 3 of the '349 patent, at issue on appeal, is directed to a pharmaceutical composition of cabozantinib (L)-malate that includes a filler, lubricant, disintegrant, and glidant, and is "essentially free"—defined as 200 ppm or less—of the 1-1 impurity. Appx79(8:15-19); Appx92(34:4-51).

II. DISTRICT COURT LITIGATION

A. MSN's Challenge

In 2012, Exelixis received FDA approval for Cometriq®, a capsule formulation of cabozantinib (L)-malate indicated to treat progressive metastatic medullary thyroid cancer. Appx3. In 2016, Exelixis received FDA approval for

Cabometyx®, a tablet formulation of cabozantinib (L)-malate now indicated to treat various cancers, including kidney, liver, and differentiated thyroid cancer. Appx3.

In 2019, MSN, a manufacturer of generic drugs, sought FDA approval to manufacture and sell a generic version of Cabometyx®. Appx2. Exelixis sued MSN under the Hatch-Waxman Act for infringement of patents not at issue in this case, including the '776 patent covering Form N-2 and U.S. Patent No. 7,579,473 covering the cabozantinib compound. *See Exelixis, Inc. v. MSN Labs. Priv. Ltd.*, No. 1:19-cv-2017 (D. Del.) ("*MSN I*").

While *MSN I* was ongoing, Exelixis continued to prosecute claims covering its inventions, filing the applications that led to the Malate Salt Patents and the '349 patent between October 2020 and June 2021. Appx74(JTX-4, 2); Appx94(JTX-1, 2); Appx143(JTX-2, 2); Appx192(JTX-3, 2). The Malate Salt Patents issued in August 2021 and the '349 patent issued in April 2022. Appx74(JTX-4, 2); Appx94(JTX-1, 2); Appx143(JTX-2, 2); Appx192(JTX-3, 2). In 2022, Exelixis filed two separate Hatch-Waxman suits against MSN asserting (1) the three Malate Salt Patents (including claim 4 of the '439 patent, claim 3 of the '440 patent, and claim 2 of the '015 patent) and (2) claim 3 of the '349 patent. Appx3. Those actions were consolidated in the district court and became the action on appeal here (the "current action").

In January 2023—after Exelixis had filed, been granted, and asserted the Malate Salt Patents and the '349 patent in the current action—the district court in *MSN I* held that, while both the compound patent and the N-2 patent were valid, MSN's ANDA products infringed only the compound patent. *MSN I*, No. 19-cv-2017, 2023 WL 315614 (D. Del. Jan. 19, 2023). Neither party appealed the district court's decision in *MSN I*.

B. Trial

The district court conducted a three-day bench trial in the current action in October 2023. MSN stipulated to infringement of the asserted Malate Salt Patents' claims, but argued they are invalid for lack of written description and obviousness-type double patenting. Appx2. MSN argued claim 3 of the '349 patent is obvious and not infringed because MSN's ANDA Products lacked a "glidant." Appx2; Appx10.

1. The Malate Salt Patents

As relevant here, the district court heard expert testimony regarding the validity of the Malate Salt Patents from Dr. Trout, Exelixis' pharmaceutical development and manufacturing expert, and Dr. Steed, MSN's pharmaceutical salt expert. Appx30-31; Appx22.

Dr. Steed testified that the specification discloses cabozantinib and the (L)-malate salt of cabozantinib. Appx1917(538:11-17). Dr. Steed admitted that "[a]

person of skill would know what crystalline meant and know that there had to be a regular repeating underlying arrangement of molecules to be crystalline." Appx1917(537:17-25). He explained that a POSA as of the priority date would typically use a polarizing microscope or x-ray powder diffraction to determine if a solid was crystalline. Appx1918(542:10-25).

Dr. Steed presented evidence of eleven alleged crystalline forms of cabozantinib (L)-malate, including eight described in patent filings by Mylan and Cipla. Appx1897(457:23-458:4). He further testified that a particular compound might have "up to 14 pure polymorphic forms." Appx1919(546:3-547:5). He explained that unless they are solvates, "all crystalline cabozantinib (L)-malate will have the same chemical formula" and "chemical makeup." Appx1918(540:1-9); Appx1922(558:24-559:3).

Dr. Steed nevertheless opined that the claims were invalid for lack of written description. When the district court asked "whether essentially your view is that, as a practical matter, no polymorph is going to be representative of another polymorph," he replied, "because each polymorph is unique, then I suppose each one is only representative of itself, would be my opinion." Appx1899(467:5-14).

Dr. Trout agreed with Dr. Steed's definition of "crystalline." Appx2049(853:7-23). He explained that, as of the priority date, a POSA would

have been able to distinguish between a crystalline material and an amorphous material using various techniques. Appx2049-2050(856:11-857:19).

Dr. Trout disagreed with Dr. Steed that there were eleven known crystalline forms of cabozantinib (L)-malate, explaining that for the alleged Mylan and Cipla forms Dr. Steed had identified, "there's no clear evidence that they're distinct forms." Appx2051-2052(861:16-863:7, 864:16-866:1). He also testified that "there's no evidence that there's actual solvates of crystalline cabozantinib (L)-malate." Appx2052(866:2-7).

Dr. Trout concluded that the claims were supported by adequate written description because "representative crystalline forms are disclosed in the specification"—specifically, Forms N-1 and N-2—and "there are common structural features disclosed in the specification" for all polymorphic forms, including N-1, N-2, and MSN's Form S. Appx2050(859:23-860:12); Appx2052(866:16-867:10). Dr. Trout explained that the common structural features—"crystalline, as opposed to amorphous"; the "formula" of the "cabozantinib malate"; and "the actual name, the chemical name also in the specification"—allow a POSA to recognize and identify other crystalline cabozantinib (L)-malate salts, and that all of those structural features were present in Forms N-1, N-2, and S. Appx2052(866:10-867:19).

2. The ’349 patent

Regarding the ’349 patent’s validity, the court heard testimony from fact witnesses Drs. Khalid Shah and Jo Ann Wilson, both named inventors on the ’349 patent. The court also heard expert testimony from Dr. MacMillan, Exelixis’ Nobel-prize winning chemistry expert; Dr. Myerson, Exelixis’ expert in separation and purification methods, crystallization, pharmaceutical formulation, and pharmaceutical manufacturing; Dr. Donovan, MSN’s expert in pharmaceutics, including solid dose drug formulation; and Dr. Lepore, MSN’s chemistry expert.

Dr. Shah, Exelixis’ Senior Vice President of Pharmaceutical Operations, testified that the A-2 Process produced cabozantinib (L)-malate API with widely varying levels of the 1-1 impurity. Appx1933(600:8-15, 603:5-23). Exelixis’ further investigation revealed that 1-1 was forming as a degradation product from the 1-3 intermediate, in addition to forming during salt formation and formulation. Appx1933(600:8-601:4); Appx46; Appx1956(693:3-695:10); Appx1934-1935(606:23-608:10). According to Dr. Shah, it was “extremely important to ensure that [Exelixis] had the lowest levels possible [of 1-1] in the API,” Appx1934(605:19-24), so Exelixis spent considerable time and effort developing the optimized B-2 Process, which reliably produces API with very low levels of the impurity, Appx1933-1934(602:1-606:5); Appx1936-1937(615:12-617:25).

Dr. Wilson, Exelixis' former Vice President of Chemistry Manufacturing and Control, confirmed that the 1-1 impurity formed in large amounts as a degradation product. Appx1925-1926(569:3-572:1). She testified that her group at Exelixis spent eight years and "an incredible amount of work" developing the B-2 Process for making cabozantinib (L)-malate API that effectively minimized levels of the 1-1 impurity. Appx1925-1926(570:1-572:1). This is the same process described in the '349 patent and used to manufacture Exelixis' commercialized cabozantinib (L)-malate products. Appx1925(568:19-22); Appx1927(576:1-24).

Dr. MacMillan testified that as of the priority date, a POSA would not have expected the 1-1 impurity to form during the five-step synthetic process described by Brown. Appx51; Appx1947(656:6-11). He further testified that a POSA would not have been motivated to control for the 1-1 impurity after completing the Brown process, because a POSA would not have expected the impurity to form in the first place. Appx46; Appx1947(656:12-18). Dr. MacMillan confirmed that the 1-1 impurity did in fact form during the Brown process at least via degradation from the 1-3 intermediate, and as a result, "[Exelixis] came up with a very different process able to effectively achieve the removal of the 1-1 impurity." Appx1950(671:2-20); Appx60.

Likewise, Dr. Myerson testified that a POSA would only expect a de minimis amount of the 1-1 impurity to be left at the end of the Brown process, because "98% of the [1-1] starting material is used up" by the end of step one. Appx52-53 (quoting Appx2012-2013(708:23-709:19)). He also testified that although a POSA would not expect the 1-1 impurity to form as a degradation product, Exelixis discovered that "20[%] of the 1-3 [intermediate] was decomposing to 1-1" during the Brown process, as evidenced in Exelixis' FDA submissions. Appx51-53; Appx1956(693:3-25); Appx1957(698:16-18).

MSN's expert Dr. Lepore, who provided opinions only on the API and did not address the alleged obviousness of the claimed formulation, opined that Brown inherently discloses cabozantinib (L)-malate API "essentially free" of the 1-1 impurity. Appx50; Appx1802(270:7-9); Appx1809(299:10-18); Appx1874(366:14-18); Appx1813(314:4-315:4). He based his opinion on three batches of API produced by Exelixis' contract manufacturer Regis, but disregarded a fourth batch made by a different contract manufacturer, Girindus, which contained much more than 200 ppm of the 1-1 impurity, on the ground that it deviated from the Brown process. Appx1818(334:11-25). Dr. Lepore conceded that Regis—like Girindus—also made changes to the Brown process, as stated in Exelixis' FDA submissions. Appx1818-1819(335:10-338:19). But he did not know what those changes were and simply "assum[ed] that [they were] extremely

minor things that [he] wouldn't even call deviation." Appx1818-1819(336:17-338:19). The three Regis batches served as the only basis for Dr. Lepore's inherency opinion. Appx1818(335:6-9).

MSN's expert Dr. Donovan admitted that the prior art did ***not*** (1) identify the 1-1 impurity as a problem in cabozantinib (L)-malate synthesis, (2) identify any mechanisms of cabozantinib (L)-malate degradation, or (3) teach how to prevent or reduce formation of the 1-1 impurity in a drug product. Appx1886-1887(415:23-417:24). Dr. Donovan did not provide any opinion on inherent obviousness; her obviousness opinion relied on Dr. Lepore's opinions regarding the level of 1-1 produced by the Brown process. Appx1875(371:17-19); Appx1881-1882(395:20-396:5); Appx1885(408:17-409:19).

C. District Court's Opinion

The district court found "MSN has not proved by clear and convincing evidence that the Malate Salt Patents lack sufficient written description" because "the specification … disclose[s] 'structural features common to the members of the genus so that one of skill in the art can visualize or recognize the members of the genus.'" Appx21; Appx23 (quoting *Ariad*, 598 F.3d at 1350). Specifically, the court found that "[d]isclosing the chemical name and formula of cabozantinib (L)-malate, as well as that the structure is crystalline, is 'an identification of structural features commonly possessed by members of the genus.'" Appx24 (quoting

GlaxoSmithKline LLC v. Banner Pharmacaps, Inc., 744 F.3d 725, 730 (Fed. Cir. 2014) (hereinafter *GSK*)). Although the district court did not determine the precise size of the genus, Appx21 n.7, it found:

- "There are three identified species in the genus of crystalline cabozantinib (L)-malate. These are Exelixis' N-1 and N-2 and MSN's Form S," Appx21;
- "There may be up to seven additional identified species in the genus of crystalline cabozantinib (L)-malate salts. These are Mylan's M-2, M-3, and M-4 and Cipla's C-2, C-3, C-4, and C-5," Appx21; and
- "The maximum potential size of any pure polymorph genus is fourteen forms," Appx21.[1]

Regarding the '349 patent, the district court held that claim 3 was not obvious because "a POSA would not expect that the 1-1 impurity would be present by the end of the Brown process," and so "would not be motivated to control for it." Appx53. The district court also rejected MSN's argument that claim 3 is inherently obvious because "MSN has not shown by clear and convincing evidence that if the Brown process is followed, it will result in a cabozantinib (L)-malate API essentially free of the 1-1 impurity." Appx46.

The court credited Exelixis' experts, Drs. MacMillan and Myerson, that the 1-1 impurity "can form as a degradation product during the Brown process," and

[1] The district court also held that certain claims of the Malate Salt Patents were not invalid for obviousness-type double patenting. Appx45.

found, based on testimony of Exelixis' fact witnesses, that the 1-1 impurity in fact formed as a degradation product during the Brown process. Appx46.

Moreover, the court found that the batch information MSN relied on to show alleged inherency "does not meet the clear and convincing standard." Appx49. Specifically, of the "four experimental batches prepared of the cabozantinib (L)-malate API," "three were prepared by the contract manufacturer Regis and one was prepared by the contract manufacturer Girindus." Appx46. The Girindus batch had levels of the 1-1 impurity as high as 411 or 600 ppm, such that it was not "essentially free" of the impurity as required by claim 3. Appx49 n.13. MSN urged the court to focus only on the three Regis batches and disregard Girindus, due to certain changes Girindus made to the Brown process. Appx2568(D.I. 169, 23). But the court found MSN had failed to show that Regis followed the Brown process. Appx46. The court cited an Exelixis FDA submission, noting "Regis stated there were some 'processing and reagent changes' to the synthetic route it had planned to follow to prepare the batches." Appx50 (quoting Appx10786(PTX-10, 9)). The court noted that MSN's expert Dr. Lepore "did not know what those changes were," Appx46, and simply testified, "I'm assuming that these [changes] are extremely minor things that I wouldn't even call deviation," Appx50 (quoting Appx1819(338:1-3)). The court did not find Dr. Lepore's testimony persuasive, and because MSN bore the burden of proof, "[could] not find that the Brown

process inherently produces a cabozantinib (L)-malate API essentially free of the 1-1 impurity because it [was] not clear to [the court] that the Regis process followed the Brown process." Appx50.

With respect to MSN's argument that "it would have been obvious for a POSA to modify the Brown process to obtain a formulation of cabozantinib (L)-malate essentially free of the 1-1 impurity," Appx51, the court found otherwise. The court found a POSA would not have expected there to be material levels of the 1-1 impurity left after the Brown process, and thus a "POSA would not be motivated to control for it" during formulation. Appx53; Appx55.[2]

The district court further held there was no infringement of the '349 patent because, although MSN's drug product contained an ingredient often used as a glidant, the court did not think Exelixis showed that it improved flow in MSN's formulation. Appx19.

SUMMARY OF ARGUMENT

1. The district court correctly found that MSN did not carry its burden on written description because the Malate Salt Patents' disclosure of the chemical name and formula of cabozantinib (L)-malate, as well as its common crystalline

[2] The Patent Trial and Appeal Board recently denied institution of inter-partes review challenging the '349 patent on similar obviousness grounds, finding no reasonable likelihood the petitioner would prevail. *Azurity Pharms., Inc. v. Exelixis, Inc.*, IPR2025-00210, Paper 11 (P.T.A.B. Jun. 4, 2025).

structure, identifies common structural features so that a POSA can visualize or recognize members of the genus. Appx23-24.

a. The evidence showed that (1) all crystalline cabozantinib (L)-malate salts share the same chemical name and formula; (2) a POSA would be able to identify whether the structure of cabozantinib (L)-malate salt is crystalline; (3) a POSA could distinguish between crystalline and amorphous cabozantinib (L)-malate; and (4) the common specification discloses methods to make the invention, including methods of preparing crystalline cabozantinib (L)-malate. The disclosure of the Malate Salt Patents was therefore sufficient for a POSA to visualize or recognize members of the genus, as the district court found.

MSN's contrary arguments ignore that "crystalline" ***is*** a common structural feature with an undisputed, well-known meaning in the art, that together with the disclosure of the chemical name (cabozantinib (L)-malate) and methods of preparing crystalline cabozantinib (L)-malate, would allow a POSA to recognize the compositions encompassed by the Malate Salt Patents' claims. This is not the "broad outline of a genus's perimeter" that MSN alleges, Br. 41, but rather a clear definition of the common structural attributes shared by all members of the claimed genus. MSN's attempts to manufacture legal error misread this Court's case law and show a fundamental misunderstanding of the particular problems faced by functional claims. Indeed, MSN's reasoning leads to the absurd and

untenable conclusion that no chemical genus claim would ever be valid under § 112(a) to the extent it covers any polymorphic solid forms.

b. Although the district court did not need to reach the issue, the evidence in the record also shows that the N-1 and N-2 forms Exelixis undisputedly disclosed are representative species supporting the genus because they exhibit the key structural property that allows a POSA to recognize the members of the genus. Namely, they are crystalline in the same way that every member of the genus is crystalline: there is a "regular repeating underlying arrangement of molecules." Appx20.

c. MSN grasps at Exelixis' later-issued patents as evidence that Exelixis sought broader claims after failing to prove MSN infringed its claims to Form N-2. But Exelixis filed claims to crystalline cabozantinib (L)-malate in its original PCT application, years before MSN even filed its ANDA. Moreover, this Court has recently clarified that later-discovered species do not cast doubt on a genus patent's written description. *In re Entresto*, 125 F.4th 1090, 1099 (Fed. Cir. 2025).

2. The district court correctly held that the prior-art Brown process does not inherently produce cabozantinib (L)-malate essentially free of the 1-1 impurity, a component of the formulation recited in claim 3 of the '349 patent.

a. Ample record evidence supports the district court's conclusion. Exelixis' witness testimony revealed large amounts of the 1-1 impurity formed as a

degradation product during the Brown process, as reflected in Exelixis' FDA submissions. Exelixis' experts explained the specific steps in the Brown process where the 1-1 impurity formed by degradation. MSN presented no evidence to negate this fact. Indeed, the testimony confirmed that Exelixis spent eight years and significant efforts designing a novel synthetic process that would reliably minimize formation of the 1-1 impurity in the cabozantinib (L)-malate API.

MSN's argument that the district court clearly erred in discounting the Regis batches is meritless. MSN based its inherency case on just three experimental non-prior art batches of API prepared by Regis which had levels of the 1-1 impurity below 200 ppm. MSN further argued that a fourth batch made by Girindus with high levels of the 1-1 impurity should be disregarded due to "deviations" from Brown. But, as stated in Exelixis' FDA submissions, Regis also made changes to the Brown process in preparing these batches. MSN was unable to explain what these changes were, and gave the court no basis, beyond its expert's mere assumption, to conclude that those changes did not take Regis outside the scope of Brown. MSN cannot have it both ways: either the deviations are not important and the Girindus batch proves that the Brown process results in variable levels of 1-1 impurity, or the deviations are important and none of the batches reflect outcomes of the Brown process. As MSN had the burden of proof and was unable to provide any detail on the deviations, it was not error for the court to decline to credit the

Regis batches as proof of inherency. Having offered no other evidence of inherency, MSN failed the clear-and-convincing standard.

b. MSN seeks to overcome its evidentiary failures at trial by arguing on appeal that the court applied a "heightened legal standard" for inherent obviousness. MSN is wrong. The district court applied the proper legal standard to the facts by requiring MSN to show that the limitation at issue—a cabozantinib (L)-malate formulation "essentially free" of the 1-1 impurity—was present in or the natural result of the combination of elements explicitly disclosed by the prior-art Brown process and other formulation references. The district court correctly found the expert testimony about whether a POSA would have ***expected*** Brown to produce API essentially free of the 1-1 impurity insufficient to support what MSN needed to show—that Brown ***in fact*** produced API essentially free of the impurity. The uncontradicted evidence that large amounts of the 1-1 impurity formed via degradation during the Brown process undermined any argument that cabozantinib (L)-malate API "essentially free" of the 1-1 impurity was the natural result. MSN's inherency case failed for lack of evidence at trial and fails again on appeal. There was no clear error or legal error in the district court's non-obviousness holding.

STANDARDS OF REVIEW

The adequacy of written-description support for a claim is a question of fact. *Ariad*, 598 F.3d at 1351. Following a bench trial, the district court's findings on

written description are reviewed for clear error. *Pozen Inc. v. Par Pharm., Inc.*, 696 F.3d 1151, 1166 (Fed. Cir. 2012). "The burden of overcoming the district court's factual findings is, as it should be, a heavy one." *Polaroid Corp. v. Eastman Kodak Co.*, 789 F.2d 1556, 1559 (Fed. Cir. 1986).

Obviousness is a question of law reviewed *de novo*, based upon underlying questions of fact reviewed for clear error following a bench trial. *Honeywell Int'l, Inc. v. United States*, 609 F.3d 1292, 1297 (Fed. Cir. 2010). A district court's inherency determination "is a question of fact" reviewed for clear error. *PAR Pharm., Inc. v. TWi Pharms., Inc.*, 773 F.3d 1186, 1194 (Fed. Cir. 2014). To rely on inherency to establish a limitation, a patent challenger must "meet a high standard" of showing that "the limitation at issue ***necessarily must be present***." *Id.* at 1195-1196.[3] A mere probability or possibility "that a certain thing may result from a given set of circumstances" cannot establish inherency. *Id.* at 1196.

Because a patent is presumed valid, MSN has the burden of proving invalidity by clear and convincing evidence. *Microsoft Corp. v. i4i Ltd. P'ship*, 564 U.S. 91, 95 (2011). The burden remains with the accused infringer and never shifts to the patentee. *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.*, 676 F.3d 1063, 1079-1080 (Fed. Cir. 2012).

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[3] All emphasis added unless otherwise indicated.

ARGUMENT

I. THE DISTRICT COURT CORRECTLY FOUND THAT CLAIMS TO CRYSTALLINE MALATE SALTS WERE NOT INVALID FOR LACK OF WRITTEN DESCRIPTION

A patentee may satisfy the written description requirement in either of two ways: (1) by disclosing a "representative number of species falling within the scope of the genus" or (2) by disclosing "structural features common to the members of the genus so that one of skill in the art can 'visualize or recognize' the members of the genus." *Ariad*, 598 F.3d at 1350 (quoting *Regents of the Univ. of California v. Eli Lilly & Co.*, 119 F.3d 1559, 1568-69 (Fed. Cir. 1997)); Appx23; Br. 37. The district court did not reach the representative-species prong because it found that "[d]isclosing the chemical name and formula of cabozantinib (L)-malate, as well as that the structure is crystalline, is 'an identification of structural features commonly possessed by members of the genus.'" Appx23-24 (quoting *GSK*, 744 F.3d at 730). That factual finding is sound and grounded in established law.

A. The District Court Properly Found That Exelixis Disclosed Structural Features Common To The Compositions Recited In The Claims

The district court found that "MSN has not proved by clear and convincing evidence that the Malate Salt Patents lack sufficient written description" because "the specification … disclose[s] 'structural features common to the members of the

genus so that one of skill in the art can visualize or recognize the members of the genus.'" Appx21; Appx23 (quoting *Ariad*, 598 F.3d at 1350). That factual finding is supported by the record, including testimony from MSN's own witnesses. MSN's attempts to show otherwise (1) dismiss the undisputed common structural features simply because they appear in the claim; (2) misread this Court's law in an effort to manufacture "legal error"; and (3) improperly focus on the properties of individual species, rather than the "common structural features" the law requires.

1. The record supports the district court's fact-finding

The district court's finding that Exelixis disclosed common structural features is supported by the intrinsic evidence and the evidence at trial, including undisputed findings supported by MSN's experts.

Claim 4 of the '439 patent is directed to crystalline cabozantinib (L)-malate salts.[4] Appx141(claim 4); Appx24. The specification states that the "disclosure relates to malate salts of [cabozantinib]," Appx127(3:36-46), and "[a]nother aspect relates to crystalline forms of [cabozantinib (L)-malate]," Appx129(8:26-28). As the district court found, "[t]he specification discloses structural features shared by all crystalline cabozantinib (L)-malate, including chemical name, formula and

[4] MSN treated claim 4 of the '439 patent as representative before the district court. *See* Appx2550-2551(D.I. 169, 5-6). Accordingly, the court's opinion focused on crystalline cabozantinib (L)-malate salts, Appx24 ("Here, the claims are directed to crystalline cabozantinib (L)-malate salts."), as does MSN on appeal.

structure." Appx21 (citing Appx94(Abstract); Appx126-127(1:26-39, 2:58-3:12) (depicting the chemical structure of cabozantinib); Appx128(5:25-6:67) (depicting the chemical structure of (L)-malic acid); Appx2052(866:10-867:3)(Trout)).

As to the term "crystalline," the district court found that "[c]rystalline is used as an adjective to describe that the cabozantinib (L)-malate has a 'regular repeating underlying arrangement of molecules,'" Appx20 (quoting Appx1917(537:22-25)(Steed)), consistent with MSN's expert testimony that a POSA "would know what crystalline meant" and would interpret it that way in the context of these patents, Appx1917(537:22-25)(Steed).

The district court further found—and MSN does not dispute—that: (1) "All crystalline cabozantinib malate share[s] the same chemical name and formula"; (2) "A POSA would be able to identify whether the structure of a polymorph is crystalline"; and (3) "A POSA could distinguish between crystalline and amorphous cabozantinib." Appx25 (citing Appx1922(558:24-559:3)(Steed); Appx1918(542:10-25)(Steed); Appx2047(846:4-19)(Trout); Appx2049(856:6-24)(Trout); Appx2052(866:10-867:3)(Trout)). The district court also noted that the specification discloses processes used to make the invention, including general methods of forming a crystalline salt and two methods of preparing crystalline cabozantinib (L)-malate. Appx24.

Those undisputed disclosures and findings sufficiently support the district court's conclusion that "[d]isclosing the chemical name and formula of cabozantinib (L)-malate, as well as that the structure is crystalline, is 'an identification of structural features commonly possessed by members of the genus.'" Appx24 (quoting *GSK*, 744 F.3d at 730).

2. MSN's attempts to challenge the district court's finding fail

With the facts against it, MSN seeks to diminish the common structural features, manufacture legal error, and deflect the Court by focusing on unclaimed properties of the salts, rather than their common structure. Those arguments misstate the facts and reflect a fundamental misunderstanding of written-description law. Critically, MSN never disputes that a POSA would be able to recognize the compositions encompassed by the claims. Indeed, if MSN's view of what is required for written description were correct, it would be impossible to claim a genus.

a. The specification and claims themselves disclose common structural features that allow a POSA to visualize or recognize the members of the genus

MSN first attacks the district court's analysis piecemeal, artificially separating and criticizing the district court's reliance on the (1) chemical name and formula of cabozantinib (L)-malate, (2) disclosure that the structure is crystalline,

and (3) methods disclosed. Br. 39-40. That separation leads to absurd arguments and fails to address the written description as a whole.

First, MSN contends that the chemical name "cabozantinib (L)-malate" cannot support the claims because it is "the *same* for both crystalline *and* amorphous forms." Br. 40 (original emphasis). Of course it is, but because the claims and specification recite ***crystalline*** cabozantinib (L)-malate, there is no "precis[ion]" lacking in the description. MSN cannot point to one part of Exelixis' claim and say the district court was wrong to rely on it, while ignoring another part of the claim that expressly resolves the alleged ambiguity.

Second, MSN contends that the term "crystalline" is insufficient because it "merely restates the genus of 'crystalline' cabozantinib (L)-malate, without *any* common structural features or defining properties for the claimed 'crystalline' forms." Br. 41. But "crystalline" ***is*** a common structural feature. It has an undisputed, well-known meaning in the art requiring a "regular repeating underlying arrangement of molecules." Appx20 (quoting Appx1917(537:22-25)(Steed)). *Ariad* requires that the written description be "sufficient to distinguish the genus from other materials." 598 F.3d at 1350. Even if there are differences among crystalline structures, a POSA would understand what crystalline means and would know what falls inside and outside the claims, as the district court found and MSN does not dispute. Appx25; *see* Appx1918(542:10-19)(Steed explaining

that, as of the priority date, a POSA would use a polarizing microscope, XRPD, or DSC to determine if a solid was crystalline); Appx2049-2050(856:25-857:12)(Trout explaining that a POSA could identify a crystalline salt without knowing what specific form the salt was in).

Thus, referring to the salts as "crystalline" is more than a "broad outline of a genus's perimeter," Br. 41 (quoting *Regents of the Univ. of Minnesota v. Gilead Scis., Inc.*, 61 F.4th 1350, 1356 (Fed. Cir. 2023)), which often occurs when a genus is described solely by its function, *see Ariad*, 598 F.3d at 1350 (criticizing functional claims for merely reciting useful results (reducing NF-κB binding to NF-κB recognition sites in response to external influences)); *Juno Therapeutics, Inc. v. Kite Pharma, Inc.*, 10 F.4th 1330, 1339 (Fed. Cir. 2021) (scFvs that bind specific targets); *Carnegie Mellon Univ. v. Hoffmann-La Roche Inc.*, 541 F.3d 1115, 1123-1126 (Fed. Cir. 2008) (disclosure of polA sequence for one bacterial source not representative of genus of recombinant plasmids "broadly defined, and only by its function, *viz.*, encoding DNA polymerase I" or "encoding an enzyme with either DNA polymerase or nick-translation activity," encompassing sequences "originating from *any* bacterial species").[5] Crystalline is not a description by

[5] *Gilead* is likewise inapposite, Br. 39. *Gilead* discusses a genus's "perimeter" in the context of a blaze marks case about whether a large chemical subgenus was adequately disclosed in a priority document describing an even larger chemical subgenus; there is no question whether the specification here

"perimeter" at all—it instead defines a common structural attribute of the members of the genus itself.

Third, MSN criticizes the district court for relying on the description of methods of preparing N-1 and N-2 because the methods are not common structural features. Br. 42-43. But the methods show possession of crystalline cabozantinib (L)-malate—the district court's reliance on that description was not legal error.

To the extent MSN argues that those descriptions do not show possession of every species, Exelixis is not required to separately disclose every possible species in the genus, *see Allergan Sales, LLC v. Sandoz, Inc*., 717 F. App'x 991, 995 (Fed. Cir. 2017) ("[e]ven a single representative embodiment can support written description of a claimed genus"), nor is Exelixis required to disclose working examples of every species, *Ariad*, 598 F.3d at 1352 ("We have made clear that the written description requirement does not demand either examples or an actual reduction to practice; a constructive reduction to practice that in a definite way identifies the claimed invention can satisfy the written description requirement."). The identification of crystalline cabozantinib (L)-malate salts—which indisputably describes structure and specifies features common to all members of the genus—is beyond sufficient to claim crystalline cabozantinib (L)-malate salts.

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contains adequate blaze marks to signal what is claimed from a broader disclosure. 61 F.4th at 1356.

b. The district court applied the proper legal standard

MSN does not dispute the common-structural-features test the district court expressly applied. Appx23; Br. 37. Instead, MSN takes issue with the district court's distinguishing certain cases involving functional claim language. But this Court has often recognized that functional claim language presents particular challenges for written description and has distinguished cases that do not rely on functional language to define a genus. *Ariad*, 598 F.3d at 1349 ("The problem is especially acute with genus claims that use functional language to define the boundaries of a claimed genus."). The district court did not apply a different standard, it simply recognized—as this Court has—that the same, proper standard can sometimes be harder to meet with functional claiming.

MSN contends that "[w]hile structural limitations may be more predictable than functional limitations in *some* fields, that is decidedly not true for polymorphs, whose unique structures and resulting physical properties are notoriously diverse and unpredictable." Br. 45. But, as detailed below, unpredictability in unclaimed features does not affect the adequacy of written description. *Infra*, pp. 46-47. Further, MSN fundamentally misunderstands the written description requirement. Functional claims are sometimes more challenging to support because the patentee is not describing what the invention ***is***, but what it ***does***—and if there is no structure-function connection disclosed in the

specification, then the patentee has failed written description by failing to describe what the invention ***is***. *See Ariad*, 598 F.3d at 1350 (explaining that written description fails when the specification does "not distinguish the genus from other materials in any way except by function, i.e., by what the genes do, and thus provided 'only a definition of a useful result rather than a definition of what achieves that result'" (quoting *Eli Lilly*, 119 F.3d at 1568)); *In re Swinehart*, 439 F.2d 210, 212 (C.C.P.A. 1971) (functional claims "define something … by what it does rather than by what it is (as evidenced by specific structure or material, for example)"). But here, Exelixis has claimed material with a common structure—crystalline cabozantinib (L)-malate salts. That is exactly what the invention ***is***. There is no failure of description.

The district court's discussions of *GSK* and *ICU Medical* reflect an accurate understanding of the applicable legal standard.

GSK. In *GSK*, this Court held that claims to dutasteride solvates were adequately described by the patent. 744 F.3d at 732. There, the specification did not have examples of dutasteride solvates—it just explained that a POSA would appreciate that organic compounds can form complexes with solvents, known as solvates, which may have a variety of crystalline forms. *Id.* at 730. Yet the Court found sufficient written description because "[d]escribing a complex of dutasteride and solvent molecules is an identification of 'structural features commonly

possessed by members of the genus that distinguish them from others,' allowing one of skill in the art to 'visualize or recognize the identity of the members of the genus.'" *Id.* at 729 (cleaned up); *see* Appx23. The Court further explained that "the claim term at issue, 'solvate,' is not functional," and so the claims "do not present the fundamental difficulty presented by the claims in virtually all of the precedents on which Defendants rely." *GSK*, 744 F.3d. at 731 (distinguishing *Ariad*, 598 F.3d at 1353; *Carnegie Mellon Univ.*, 541 F.3d at 1123-1124; and *Eli Lilly*, 119 F.3d at 1562-1563, among others).

The district court recognized the similarity between *GSK* and this case:

> As in *GSK*, the limitation at issue here is structural, not functional. Neither party disputes that crystalline is a structural limitation. Although there are different crystalline polymorphs of cabozantinib (L)-malate, the claims "involve[] no performance property … and hence raises no issue of insufficient structural, creation-process, or other descriptions to support such a property."

Appx24 (quoting *GSK*, 744 F.3d at 729-730).

MSN tries to explain *GSK* away on the grounds that the complex was not the point of novelty for the invention. Br. 46-49. But the *GSK* decision did not turn on any "point of novelty"[6]—it simply recognized that the recitation of dutasteride was a "key structural component" in the disclosed "complex of dutasteride

[6] MSN's pincites here, Br. 47, are inaccurate, but it appears to be citing the Court's summary of the district court findings, not the Court's written description analysis.

molecules and solvent molecules," supporting the conclusion that the specification included "a precise definition, such as by *structure*," for the claimed genus. *GSK*, 744 F.3d at 730 (quoting *Ariad*, 598 F.3d at 1350 (original emphasis)).

Additionally, while MSN protests that ***cabozantinib*** is not novel, Br. 47, the ***cabozantinib (L)-malate salt*** is novel—as MSN did not dispute at trial. The specific discovery of the (L)-malate salt is part of the invention in this case. Appx127(3:26-32) ("Applicants have found a salt form of the drug [cabozantinib] that has suitable properties for use in a pharmaceutical composition for the treatment of a proliferative disease such as cancer. The novel salt form of the invention exists in crystalline and amorphous forms."); Appx129(7:32-36) ("The Compound (I) salt itself, and separately its crystalline and amorphous forms, exhibit beneficial properties over the free base and the other salts of [cabozantinib]."). That is what the district court specifically found: "Here too, the key feature of the genus is the chemical formula and structure of crystalline cabozantinib (L)-malate." Appx25. MSN is wrong that the "alleged utility of the claimed crystalline forms" is limited to features exhibited only by Forms N-1 and N-2. Br. 48-49; *see* Appx128-129(6:56-8:24).

Further, MSN's attempt to distinguish the "well-known and relatively small" genus of pharmaceutically acceptable solvents at issue in *GSK* from the alleged

"virtually infinite" number of crystal growth structures here is not supported by the evidence. Br. 48.

First, Exelixis' claims are not directed to a "virtually infinite" genus. MSN cites Dr. Trout's testimony completely out of context. Dr. Trout testified:

> Q. And then as the prior art taught – and here [in Dr. Trout's expert report] you quote. Okay? The range and combinations of crystal growth structures are virtually infinite and there is no way to guarantee the preparation of additional polymorphs of a substance, much less the generation of all of them. Is that still your opinion, today?
>
> A. Yes.

Appx2066(922:10-17). This testimony related to prior art without the benefit of Exelixis' teachings. Appx2069-2070(935:8-937:10)(Trout). Moreover, what is "virtually infinite" are the possible crystalline structures available ***generally***. But that does ***not*** mean that a ***particular substance***—in this case, cabozantinib (L)-malate—has a "virtually infinite" number of crystal forms.

Instead, as Dr. Steed testified and the district court specifically found, "[t]he maximum potential size of any pure polymorph genus is fourteen forms." Appx21 (citing Appx1919(547:2-5)). Although the district court did not determine the precise size of the genus, Appx21 n.7, it specifically found that Exelixis' N-1 and N-2 and MSN's Form S were members of the genus and "[t]here may be up to

seven additional identified species" from Mylan and Cipla, Appx21 (citing Appx1896-1897(455:5-456:12)(Steed)).[7]

MSN does not challenge these factual findings—nor could it, as they are based on its own expert's testimony.[8] Dr. Trout's testimony is not to the contrary. There is no basis for MSN's argument that the genus here is "virtually infinite."

Second, MSN makes a false comparison: what was found in *GSK* to be "well-known and relatively small" was the genus of pharmaceutically acceptable ***solvents*** with which to make the claimed genus of dutasteride ***solvates***. But the claims upheld in *GSK* cover ***any*** crystalline form of the ***solvates***, just like the claims at issue here cover any crystalline form of the cabozantinib (L)-malate.

ICU Medical. Contrary to MSN's assertion, *ICU Medical* is neither "closely analogous" nor "directly on point" to the facts here, Br. 49, and the district court did not legally err in determining that it was "not applicable," Appx27. In *ICU Medical, Inc. v. Alaris Medical Systems, Inc.*, the patentee sought "spikeless" claims effectively covering a genus including spiked and spikeless medical valves. 558 F.3d 1368, 1378 (Fed. Cir. 2009). Spiked and spikeless medical valves have

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[7] Indeed, before the district court, MSN argued that the genus is 11 species. Appx21 (citing Appx2553(D.I. 169 at 8) (addressing "the 11 reported crystalline cabozantinib (L)-malate salts" discussed in "[t]he patent literature")).

[8] To the extent MSN argues on reply that this statement does not include solvates, Dr. Trout testified there was no evidence of the existence of any solvated forms. Appx2052(866:2-7).

different structural features, based on whether they include the spike element. This Court concluded that the spikeless claims lacked written description because the patentee had "failed to point to any disclosure in the patent specification that describe[d] a spikeless valve." *Id.* at 1379. Further, "the specification in *ICU Medical* attributed a particular function to the spike—piercing a seal inside the valve—that could not be accomplished without a spike." *Allergan USA, Inc. v. MSN Labs. Priv. Ltd.*, 111 F.4th 1358, 1375 (Fed. Cir. 2024).

Unlike the spikeless claims in *ICU Medical*, there is no dispute here that all crystalline cabozantinib malate forms, including N-1 and N-2, contain the same structural feature of being crystalline (i.e., having "a 'regular repeating underlying arrangement of molecules,'" Appx20), and the same chemical formula and name—all of which are disclosed in the specification. Appx24. MSN argues that the description is insufficient because "the specification here fails to describe the *structure* of any crystalline form lacking the identifying properties unique to N-1 and N-2." Br. 51 (emphasis by MSN). But that is wrong: Requiring Exelixis to describe specific structures that differentiate species is tantamount to requiring Exelixis to disclose all species, which is not the law. The law requires disclosure only of ***common*** structure across species.[9]

[9] To the extent MSN contends Exelixis must specifically describe more species, that (1) does not affect the district court's decision regarding whether

Tronzo & Eli Lilly. MSN next cites two cases for the unremarkable proposition that the full scope of the genus, including structurally claimed genera, must be supported by written description. Br. 52-54 (citing *Tronzo v. Biomet, Inc.*, 156 F.3d 1154 (Fed. Cir. 1998); *Eli Lilly & Co. v. Teva Pharms. USA, Inc.*, 619 F.3d 1329, 1344-1345 (Fed. Cir. 2010)). The district court did not hold otherwise.

In *Tronzo*, the claims were directed to artificial hip sockets with an "acetabular cup pro[s]thesis." 156 F.3d at 1156. The Court found the specification disclosed "only two species of cups: an 'eccentric cup,' which has a top lip shorter than the bottom lip, and a 'true' cup, with all sides being equal," and "the only reference in the [asserted] patent's specification to different shapes [wa]s a recitation of the prior art." *Id.* at 1159. "Instead of suggesting that the [asserted] patent encompasses additional shapes, the specification specifically distinguishes the prior art as inferior and touts the advantages of the conical shape of the [claimed] cup." *Id.* The Court held that "[s]uch statements make clear that the [asserted] patent discloses *only* conical shaped cups and nothing broader." *Id.*

Here, there are no such statements disclaiming other species of crystalline cabozantinib (L)-malate (indeed, prior-art cabozantinib malate salts did not exist). To the contrary, the specification states that "crystalline forms … ***include*** the N-1

Exelixis disclosed common structure, and (2) is wrong for reasons discussed *infra*, pp. 51-53.

and/or the N-2 crystalline form," indicating that the disclosure is not limited to N-1 and N-2. Appx129(8:26-30). "[A] specification's focus on one particular embodiment or purpose cannot limit the described invention where that specification expressly contemplates other embodiments or purposes." *Allergan USA*, 111 F.4th at 1374 (quoting *ScriptPro LLC v. Innovation Assocs., Inc.*, 833 F.3d 1336, 1341 (Fed. Cir. 2016)).

As for *Eli Lilly*, this Court explained in *GSK* that the "claims in *Eli Lilly* … , covered particle sizes before and after formulation into tablets, but the specification addressed only pre-formulation size." *GSK*, 744 F.3d at 731 (discussing *Eli Lilly*, 619 F.3d at 1344-1345). That is "quite different" from a situation where, as here, "the claim is no broader in scope than the written description" and the "passage from the written description matches the claim scope." *Id*. Here, the specification explains:

- "This disclosure relate[s] to … the (L)-malate salt of [cabozantinib], (Compound I)." Appx128(6:56-61).
- "The Compound (I) salt itself, and separately its crystalline and amorphous forms, exhibit beneficial properties over the free base and the other salts of [cabozantinib]." Appx129(7:32-34).
- "Compound (I) has favorable pharmaceutical properties in regard to stability (such as storage stability) and crystallinity over other forms of [cabozantinib]." Provisional App. No. 61/145,421 ¶[0021]; Appx126 (incorporating provisional by reference).

Exelixis' further description of two examples in detail does not diminish its disclosure of crystalline cabozantinib (L)-malate salts generally, which matches the claim scope.

c. The district court did not err in finding written description despite alleged differences in some unclaimed physical properties

Relying on a grab-bag of alleged differences, MSN contends that the district court was wrong to "discount[]" evidence that different polymorphs of crystalline cabozantinib (L)-malate have "different densities, melting points, solubilities, hygroscopicity, vapor pressure, and stability." Br. 54 (quoting Appx25-26). But any variability in those ***unclaimed properties*** is irrelevant. Exelixis has not defined its claims in reference to those properties, but through the common structure shared by polymorphs within the scope of the claims. *GSK*, 744 F.3d at 729-730 ("No matter which construction is adopted, the term 'solvate' involves no performance property (the claimed compound need not perform an identified function or produce an identified result) and hence raises no issue of insufficient structural, creation-process, or other descriptions to support such a property.").

MSN points to the list of features in *Ariad*, but that case says that in the chemical arts, common structural features include "structure, formula, chemical name, physical properties, ***or*** other properties, of species falling within the genus sufficient to distinguish the genus from other materials." 598 F.3d at 1350. A

genus need not have common structure across ***all*** of those dimensions as long as the common structural features the patentee describes are sufficient to allow a POSA to recognize the genus. The district court therefore correctly rejected MSN's argument.

3. MSN's position would upend settled law

MSN's position would work a sea change in the law. For example, claims to "pharmaceutical salts thereof"—which are silent regarding amorphous and crystalline forms and thus presumably encompass both—are routinely upheld. *E.g.*, *Forest Labs., LLC v. Sigmapharm Labs., LLC*, 918 F.3d 928, 937-938 (Fed. Cir. 2019) (district court did not clearly err in finding written description adequate for claims to a pharmaceutical composition containing asenapine "or a pharmaceutically acceptable salt thereof"); *Bristol-Myers Squibb Co. v. Aurobindo Pharma USA Inc.*, 477 F. Supp. 3d 306, 353 (D. Del. 2020) (upholding validity over § 112 challenge to claim directed to compound or its pharmaceutically acceptable salt though specification did not include examples describing how to make any salts (let alone crystalline forms thereof) of compound), *aff'd sub nom. BMS v. SigmaPharm Labs., LLC*, 858 F. App'x 359 (Fed. Cir. 2021); *Merck Sharp & Dohme, LLC v. Mylan Pharms. Inc.*, Civ. A. No. 19-101, 2022 U.S. Dist. LEXIS 195204, at *113 (N.D. W. Va. Sept. 21, 2022) (upholding validity over § 112 challenge to claim to salt of pharmaceutical compound "or a hydrate thereof").

If MSN were correct, a challenger would be able to invalidate claims for lack of written description simply by pointing to any difference in any property between members of the genus, regardless of whether the genus was defined by or the claims even mentioned that property. It would gut the idea of representative disclosure: MSN's expert admitted that his opinion would result in the extreme result that one crystalline form could never be representative of another, even if they are "quite closely related," Appx1896(452:2-9)(Steed): "I suppose each [form] is only representative of itself, would be my opinion," Appx1899(467:5-14)(Steed). The law is not so rigid: It allows genus claims as long as common structure or representative species are sufficiently disclosed to allow a POSA to visualize or recognize the genus, which is exactly what Exelixis did here.

4. MSN incorrectly characterizes the timing of the Malate Salt Patents

MSN incorrectly implies that Exelixis returned to the Patent Office after failing to prove MSN infringed its Form N-2 claims to get broader claims that would improperly encompass MSN's allegedly novel Form S. *E.g.*, Br. 36-37. But the specific applications that issued as the Malate Salt Patents were filed on October 14, 2020, January 14, 2021, and February 9, 2021, Appx94(JTX-1, 2); Appx143(JTX-2, 2); Appx192(JTX-3, 2)—years before the 2023 judgment that MSN's ANDA products did not infringe the '776 patent. Furthermore, Exelixis first filed claims to crystalline cabozantinib (L)-malate as long ago as January 15,

2010 with the original '194 PCT application, almost a decade before MSN filed its ANDA in 2019 and eight years before MSN filed its application describing Form S on December 7, 2017. Appx9413(JTX-7, 51). There is nothing improper about Exelixis pursuing narrow claims first and continuing prosecution to the full extent of the disclosure provided. Exelixis gained no additional patent term, and the as-filed claims covering crystalline cabozantinib (L)-malate have been published since July 2010.

5. MSN's remaining arguments fail

MSN repeatedly states that the Exelixis inventors "did not invent any crystalline form of cabozantinib (L)-malate other than Forms N-1 and N-2." *E.g.*, Br. 57. Although the district court used that phrasing, it is evident from context that it means only that Exelixis did not disclose ***making*** other forms. The finding is derived from Dr. Trout's testimony, where he first was asked "as a factual matter" whether Exelixis "invent[ed]" Form S, the particular form of crystalline cabozantinib (L)-malate used by MSN in its ANDA product. Appx2061(902:11-18). He was not offering an opinion as to who invented the asserted claims. And whether Exelixis made the later-discovered Form S does not cast doubt on the written description of Exelixis' claims. *Entresto*, 125 F.4th at 1099. The use of the word "invent" in the context of particular species of polymorphs does not erase

the specification's disclosure of crystalline cabozantinib (L)-malate or render the working examples in the specification unrepresentative.

MSN also touts its patent on Form S. Br. 18. But MSN's ability to patent Form S does not show a lack of written description of Exelixis' genus claims. It is black-letter law that a species may be patentable over a genus. That does not mean the genus was not described; just that something different about the species rendered it patentable. *Entresto*, 125 F.4th at 1098-1099; *see In re Baird*, 16 F.3d 380, 382 (Fed. Cir. 1994) ("The fact that a claimed compound may be encompassed by a disclosed generic formula does not by itself render that compound obvious."); *cf. CFMT, Inc. v. Yieldup Int'l Corp.*, 349 F.3d 1333, 1340 (Fed. Cir. 2003) ("Improvement and selection inventions are ubiquitous in patent law; such developments do not alone cast doubt on enablement of the original invention.").

B. In The Alternative, Exelixis Disclosed A Representative Number Of Species

Like the district court, this Court need not reach the question of representative species because Exelixis' description of common structural features is sufficient. Nevertheless, the record shows that Exelixis properly disclosed sufficient representative species, namely the N-1 and N-2 crystalline forms. Therefore, if the Court reaches the question and does not resolve it against MSN, it should remand for the district court to address the issue.

Representative species need only be representative of the claimed structures, and a single species can be representative of a genus. *Allergan Sales*, 717 F. App'x at 995. Here, the claims are directed to crystalline cabozantinib (L)-malate salts. The disclosed N-1 and N-2 forms are representative because they share the chemical formula—cabozantinib (L)-malate—and crystallinity, which are the relevant features for the claims. Moreover, this is not a genus with thousands of members: it contains three identified species and up to seven additional crystalline species, and "[t]he maximum potential size of any pure polymorph genus is fourteen forms." Appx21.

MSN contends that Forms N-1 and N-2 cannot be representative because they "abide in a corner of the genus" and the specification must "'reflect the structural diversity of the claimed genus,' regardless of whether such features are claimed." Br. 58-60 (quoting *AbbVie Deutschland GmbH & Co. v. Janssen Biotech, Inc.*, 759 F.3d 1285, 1300-1301 (Fed. Cir. 2014)). But *AbbVie* does not stand for the proposition that a patentee must describe representative species on every possible axis of comparison, or for unclaimed features.

In *AbbVie*, the genus was a "class of fully human antibodies that are defined by their high affinity and neutralizing activity to human IL-12, a known antigen." 759 F.3d at 1299. AbbVie's specification disclosed several structurally similar species derived from the same antibody. The Court rejected AbbVie's argument

that "structural differences are legally irrelevant" and that it could "rely on the k_{off} rates to show representativeness," because "[t]he k_{off} rate is merely a desired result, rather than the actual means for achieving that result." *Id.* at 1301. The Court explained that "the structure of the antibody determines its antigen binding characteristic," so "[i]n order to demonstrate that it has invented what is claimed, AbbVie's patents must adequately describe representative antibodies to reflect the structural diversity of the claimed genus." *Id*. *AbbVie* thus stands for the proposition that, even when seeking to show written description under the representative species prong, a patentee claiming a genus with ***functional*** language must show species representative of ***structures*** that achieve that function. Here, Exelixis' claims cover compounds with a particular structure—crystalline cabozantinib (L)-malate salts—and it undisputedly described two compounds with that structure. Those are sufficient representative species even under *AbbVie*.

Finally, MSN complains that the district court improperly faulted MSN for failing to explain why variations in physiochemical properties made N-1 and N-2 "so different from other forms" of crystalline cabozantinib (L)-malate "that they are unrepresentative." Appx26. But MSN does not assert that any other alleged forms of crystalline cabozantinib (L)-malate would have properties so varied that they could not be used in pharmaceutical compositions as claimed—indeed, MSN represented to the FDA that its Form S was bioequivalent to Forms N-1 and N-2

and suitable for pharmaceutical development. Appx2070(937:21-938:5). Nor did MSN satisfy its burden of showing that the alleged variations were so significant as to render the N-1 and N-2 species insufficiently representative.

II. THE DISTRICT COURT CORRECTLY FOUND THAT CLAIM 3 OF THE '349 PATENT IS NOT OBVIOUS

The district court upheld claim 3 of the '349 patent against both of MSN's obviousness arguments, finding that (1) the prior-art Brown process does not inherently produce a cabozantinib (L)-malate API essentially free of the 1-1 impurity; and (2) it would not have been obvious for a POSA to modify the Brown process and obtain a formulation of cabozantinib (L)-malate essentially free of the 1-1 impurity. Appx48; Appx51. On appeal, MSN challenges the court's non-obviousness holding only on the grounds that the "essentially free" limitation was inherent in the prior art, Br. 9, but MSN can identify no error, let alone clear error or legal error, in the court's decision. The district court's holding of non-obviousness should be affirmed.

A. Substantial Evidence Supports The District Court's Holding That Claim 3 Of The '349 Patent Is Not Inherently Obvious

The district court held that claim 3 of the '349 patent is not inherently obvious because, as a matter of fact, "MSN has not shown by clear and convincing evidence that if the Brown process is followed, it will result in a cabozantinib (L)-malate API essentially free of the 1-1 impurity." Appx46. Specifically, "there is

neither clear and convincing experimental data nor expert testimony about the underlying scientific principles." Appx49. That holding was firmly grounded in the court's factual determinations and supported by the record evidence.

First, the district court found "[the] 1-1 impurity can form as a degradation product during the Brown process." Appx46. In fact, "Exelixis presented evidence that the 1-1 impurity ***did*** form as a degradation product during the Brown process." Appx50-51. Specifically, an intermediate compound in the A-1 and A-2 (Brown) Processes was found "to decompose to form large amounts of the 1-1 impurity." Appx46. MSN presented no evidence to show that the 1-1 impurity did not in fact form via degradation during Brown. Appx50-51. MSN does not address the evidence of degradation formation of 1-1 in its opening brief, and that evidence alone is fatal to MSN's inherent obviousness case.

Second, with respect to the batch information relied upon by MSN—which was limited to three experimental non-prior-art batches of API prepared by Regis—the district court found "[t]he Regis batches did not follow the Brown experimental process." Appx46. Accordingly, the court found the Regis batches did not support that the Brown process inherently produces a cabozantinib (L)-malate API essentially free of the 1-1 impurity. Appx50. The absence of experimental data to support MSN's inherency case is reason enough to reject it. MSN failed to overcome both serious evidentiary gaps in its inherent obviousness

case at trial, and fails to overcome them now on appeal. The district court's decision was not factually or legally erroneous.

1. The record evidence showed that the 1-1 impurity could and did form via degradation

First, the district court found "[t]he 1-1 impurity could have formed as a degradation product," based on evidence Exelixis presented that the impurity "did form as a degradation product during the Brown process." Appx50-51. As the court explained, "Dr. Myerson testified that '20[%] of the 1-3 [intermediate] was decomposing to 1-1.'"[10] Appx51 (quoting Appx1956(693:11-12)). In post-trial briefing, MSN argued "there is no evidence that Exelixis' work 'discovered' the 1-1 impurity formed in any meaningful amount (and certainly not more than 200 ppm) when the Brown Example 1 process was followed." Appx2793(D.I. 177, 17) (emphasis omitted). MSN repeats this argument on appeal. Br. 75. But this argument—which improperly attempts to shift the burden of proof to Exelixis—was already rejected by the district court as rebutted by credible testimony and evidence. Appx51.

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[10] MSN criticizes the court for relying on Dr. Myerson's testimony about degradation formation of the 1-1 impurity during the A-1 and B-2 Processes, on the grounds that these are different processes from the A-2 (Brown) Process. Br. 75. But MSN's criticism is groundless: Dr. Myerson testified that the degradation problem persisted during the A-2 Process, and the court also cited the fact witness testimony of Drs. Wilson and Shah that the 1-1 impurity was in fact forming as a degradation product during the A-2 Process. Appx51 (citing Appx1925(569:16-25); Appx1933(600:8-601:4)).

Specifically, the district court relied upon the following evidence that the 1-1 impurity formed at material levels as a degradant during the Brown process:

- Dr. Wilson's testimony that during the A-2 Process, the "competing decomposition pathway" of the 1-3 intermediate compound to the 1-1 impurity "***could not be controlled***." Appx1925(569:16-25).

- A document Exelixis submitted to the FDA confirming this fact. Appx10845(PTX-35, 9).

- Dr. Shah's testimony that during the A-2 Process, the 1-1 impurity was "particularly challenging to control" as a degradant. Appx1933(600:8-601:4).

- The testimony of Dr. Myerson that during the A-1 Process, "20[%] of the 1-3 [intermediate] was decomposing to 1-1," and that this problem persisted in the A-2 Process. Appx1956(693:3-13, 694:5-12).

Indeed, Exelixis spent eight years and significant resources to address the problem of degradation formation of 1-1 in the API, and would not have done so if the problem did not exist. *See* Appx1956(692:23-695:14); Appx1933-1934(602:1-606:5); Appx1926-1927(575:24-576:24); Appx1925-1926(568:2-572:1). The degradation product testimony alone defeats any argument that the Brown process inherently produces API essentially free of 1-1. The district court's findings on inherency are thus supported by substantial evidence and should not be disturbed.

2. The record evidence supports the district court's conclusion that Regis deviated from the Brown process

Second, the district court did not clearly err in finding that MSN failed to carry its burden of proving that Regis evidenced the inherent result of the prior art Brown process. Appx50. As the court explained, Exelixis' FDA submissions stated that Regis made some "'processing and reagent changes' to the synthetic route Regis had planned to follow to prepare the batches." Appx50 (quoting Appx3115(DTX-38, 9)). MSN's expert Dr. Lepore "testified that the Brown process and Regis process were the same," but was unable to explain what processing and reagent changes were made by Regis and referenced in Exelixis' FDA submissions, and simply testified, "I'm assuming that these [changes] are extremely minor things that I wouldn't even call deviation." Appx50 (quoting Appx1819(338:1-3)). Accordingly, MSN gave the court no basis beyond the assumption of its expert to conclude that the three Regis batches—MSN's only purported experimental evidence of inherency—actually followed Brown. Further, when Dr. Myerson was asked at trial whether "[t]here were no deviations in the Regis process from … Brown," Appx2033(790:4-5), he responded, "I don't believe that's what it says in the document. I've seen a document at some point that does say ***there were deviations***. And, actually, Dr. Lepore was cross-examined about that and was shown ***a document that was up in Court that said there were deviations***," Appx2033(790:6-10). The record evidence and trial

testimony thus support the district court's conclusion that Regis deviated from Brown.

MSN itself emphasized the importance of deviations from Brown when attacking Exelixis' reliance on the batch made by Girindus, which had high levels of the 1-1 impurity. Appx2568-2570(D.I. 169, 23-25). But it now objects to the court's reasonable consideration of the fact that deviations from Brown were made by ***both*** manufacturers. Br. 7, 30. MSN cannot cherry-pick the Girindus and Regis batches. It was not clear error for the district court to find that MSN had failed to carry its burden when (1) the Girindus batch refuted MSN's inherency argument; (2) MSN's distinction of Girindus stressed the significance of deviating from Brown; (3) MSN admitted that Regis also deviated from Brown; and (4) MSN did not clearly show what the Regis deviations were, let alone establish that they made no difference. MSN argues that "Exelixis did not produce any" evidence of what these "purported 'changes' [made by Regis]" were, Br. 63, but it was MSN who had the burden to show by clear and convincing evidence that the Regis batches represented the inherent result of the Brown process. MSN failed to meet this burden. *See* Appx49-50.[11]

[11] MSN contends that "Exelixis conceded that Regis followed the Brown process." Br. 61 (emphasis omitted). But Exelixis disputed that Regis represented the inherent result of the Brown process and noted the "processing and reagent changes" Regis made in its proposed responsive findings of fact. *See* Appx2763-

The district court's holding is consistent with this Court's prior decisions that "[i]nherency may not be established by probabilities or possibilities, and the mere fact that a certain thing ***may*** result from a given set of circumstances is not sufficient." *Persion Pharms. LLC v. Alvogen Malta Operations Ltd.*, 945 F.3d 1184, 1191 (Fed. Cir. 2019) (cleaned up) (original emphasis). For example, in *Hospira, Inc. v. Amneal Pharmaceuticals, LLC*, the district court declined to find inherency based on two experimental examples of stability data at the claimed concentration formulation, and no expert testimony regarding the scientific principles underlying the alleged inherent property. 285 F. Supp. 3d 776, 800 (D. Del. 2018), *aff'd*, 748 F. App'x 1024 (Fed. Cir. 2019). Here, the evidence of inherency is even weaker, with no experimental data to credibly support MSN's case and contrary expert testimony regarding scientific principles, such as degradation formation of the 1-1 impurity, that undermines the alleged inherent property.

Even if the district court had found that the three Regis batches followed Brown and ignored the Girindus batch, three samples would be insufficient to

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2764(D.I. 176, ¶74). In any case, whether the parties agreed about Regis following Brown is inconsequential in view of the well-settled principle that "[o]n judicial review, the correctness of the decision appealed from can be defended by the appellee on any ground that is supported by the record, whether or not the appellant raised the argument." *Rexnord Indus., LLC v. Kappos*, 705 F.3d 1347, 1356 (Fed. Cir. 2013).

prove inherency given the extensive evidence that the Brown process was variable and formed large amounts of the 1-1 impurity by degradation. Appx46; Appx51; Appx2032(786:2-788:7); *Hospira*, 285 F. Supp. 3d at 800. Thus, regardless of whether the Regis batches and/or the Girindus batch followed Brown, declining to find inherency on this record was entirely correct.

B. The District Court Applied The Proper Legal Standard For Inherency In Rejecting MSN's Obviousness Argument

"[T]he use of inherency … must be carefully circumscribed in the context of obviousness." *PAR Pharm., Inc. v. TWi Pharms., Inc.*, 773 F.3d 1186, 1195 (Fed. Cir. 2014). MSN does not dispute that to show inherency of an element as part of its obviousness argument, it needed to show that "the limitation at issue necessarily must be present, or the natural result of the combination of elements explicitly disclosed by the prior art." Br. 71 (quoting *Hospira, Inc. v. Fresenius Kabi USA, LLC*, 946 F.3d 1322, 1329 (Fed. Cir. 2020) (emphasis omitted)). That is the same test the district court applied. Appx48.

Attempting to manufacture a legal issue where there is none, MSN now incorrectly argues that by requiring MSN to show that the Brown process does not form the 1-1 impurity through degradation, the district court applied a standard for inherency that was "too exacting." Br. 70, 72. But the district court only required MSN to establish the legal requisite for its inherency argument. MSN argued that API made by the Brown process was essentially free of 1-1, and that if formulated

into the claimed pharmaceutical composition, such API would still be essentially free of 1-1. MSN therefore needed to show, as an initial matter, that API essentially free of 1-1 was the natural result of the Brown process. Appx49.[12]

Although the district court considered MSN's argument that the 1-1 impurity did not form "in any meaningful amount (and certainly not more than 200 ppm) when the Brown Example 1 process was followed," Appx51 (quoting D.I. 177 at 17), it credited Dr. Myerson's testimony that "20[%] of the 1-3 [intermediate] was decomposing to 1-1" during the A-1 Process, Appx51 (quoting Appx1956(693:11-12)), and that this problem persisted during the A-2 Process, Appx1956(693:3-13, 694:5-12). Degradation, as the trial evidence showed, was one route by which the 1-1 impurity formed in the API. Appx46. MSN thus failed to show that the impurity would ***not*** form, by degradation or otherwise, at material levels in API made by the prior art Brown process. Appx46. MSN's argument that "there is no evidence suggesting that *more than 200 ppm* of the impurity formed [via

[12] The asserted claim recites a "pharmaceutical composition"—i.e., a formulation of cabozantinib (L)-malate ***with additional components***—essentially free of 1-1. MSN's argument regarding the alleged inherent absence of the 1-1 impurity in API produced by the Brown process was therefore not an anticipation argument but part of an obviousness argument. Because MSN failed to show API essentially free of 1-1, the district court did not need to address other problems with MSN's argument, such as testimony establishing that having ***API*** essentially free of 1-1 does not guarantee a ***formulation*** essentially free of 1-1. Appx1958(701:19-702:7); Appx2020(739:25-740:11); Appx1955(689:17-690:6).

degradation], as required to take the product outside the scope of the claim," has it backwards. Br. 75 (emphasis by MSN). As the district court stated, "it is MSN's burden, not Exelixis', to show that the Brown process does not form the 1-1 impurity through degradation." Appx51; *accord Cyclobenzaprine*, 676 F.3d at 1079-1080.

MSN's argument that the district court applied a "heightened legal standard" to the expert testimony is equally meritless. Br. 9. MSN points to so-called "corroborative scientific evidence"—namely, expert testimony on whether a POSA would have ***expected*** the Brown process to result in API with de minimis amounts of the impurity—and asserts that the district court ***legally*** erred in holding this evidence insufficient to show inherency. Br. 9, 35. But calling the testimony "corroborative" does not make it so, nor does calling this a legal issue make it one. The district court properly relied on Dr. Myerson's scientific explanation that the 1-1 impurity formed as a result of degradation, including from the 1-3 intermediate, during the Brown process. Appx51. In contrast, the expert testimony cited by MSN did not relate to what actually occurred during the Brown process. Appx46; Appx50-51. Based on these facts, the court held that "MSN's expert testimony about how the underlying science of the Brown process leads to an API essentially free of the 1-1 impurity does not meet the clear and convincing

evidence standard."[13] Appx50. The district court therefore applied the correct legal standard for inherency to the evidence and deemed MSN's expert testimony insufficient to meet that standard. There was no legal error.

At bottom, MSN's inherency argument requires the Court to ***assume*** that the three Regis batches, but not the Girindus batch, followed Brown (despite evidence that both Regis and Girindus made deviations) and to ***assume*** that the 1-1 impurity necessarily did not form as a degradation product in an amount above 200 ppm in API prepared according to the Brown process (despite evidence that large amounts of 1-1 formed by degradation and that Exelixis invested years of research into avoiding that pathway). Appx50-51. The district court did not commit legal error in finding such unsupported assumptions inadequate, especially where credible evidence contradicts those assumptions.

MSN cites *Santarus, Inc. v. Par Pharmaceutical, Inc.*, 694 F.3d 1344 (Fed. Cir. 2012), but *Santarus* is distinguishable. *Santarus* affirmed a judgment of obviousness where the evidence showed that the claimed blood serum concentrations were the natural result of known prior-art formulation and dosages

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[13] MSN claims that its expert testimony "went beyond merely articulating an 'expectation'" and "unequivocally" opined on the ultimate issue of inherency. Br. 73-74. But "[n]othing in the rules or in [the Federal Circuit's] jurisprudence requires the fact finder to credit the unsupported assertions of an expert witness." *Rohm & Haas Co. v. Brotech Corp.*, 127 F.3d 1089, 1092 (Fed. Cir. 1997).

and there was no factual finding or credible evidence otherwise. 694 F.3d at 1354. Here, MSN failed to establish that the Brown process naturally results in a formulation of cabozantinib (L)-malate essentially free of 1-1, there was evidence to the contrary, and the district court found against MSN. The only legal error is MSN's disregard of the standard of review, which requires deference to the district court's underlying factual findings.

Likewise, MSN's reliance on *SmithKline Beecham Corporation v. Apotex Corporation*, 403 F.3d 1331 (Fed. Cir. 2005) is misplaced. *SmithKline* was an inherent anticipation case in which the defendant argued the prior art process of making paroxetine hydrochloride (PHC) anhydrate inherently resulted in trace amounts of the claimed PHC hemihydrate. 403 F.3d at 1341. The district court found no inherent anticipation because the defendant had failed to show that it was impossible to make pure PHC anhydrate. *Id*. at 1343. The *SmithKline* Court held that this standard of proof was "too exacting"; it would have been sufficient for the defendant to show that the PHC hemihydrate was "the natural result flowing from the operation as taught in the prior art." *Id*.

The district court here never required MSN to show that it was ***impossible*** for the Brown process to result in API that was not essentially free of the 1-1 impurity. It only required clear and convincing evidence that API "essentially free" of 1-1 was the natural result of the Brown process. Appx51. Degradation

was a major route by which the 1-1 impurity formed, and the court credited Dr. Meyerson's testimony regarding the degree of degradation. Appx50-51. Against that backdrop, the court merely held MSN to the burden of establishing that the Brown process necessarily resulted in API with 200 ppm or less of 1-1. MSN failed to carry that burden, let alone show the inherency of a formulation essentially free of the 1-1 impurity. The Court should reject MSN's invitation to overwrite the district court's careful fact-finding.

CONCLUSION

The judgment should be affirmed.

Respectfully submitted,

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